Remarks

The present invention is directed to the discovery that an effective and safe immune response against *Campylobacter* can be raised in birds, in ovo, by administration of live Campylobacter cells as immunogen. It has also been surprisingly discovered that such vaccination is safe, and does not harm the developing bird. Applicant respectfully believes that this invention is neither present in the prior art, nor is it suggested by any combination of teachings found in the prior art. Support for new Claim 21 (for human food consumption) is found throughout the specification, see also the Background of the Invention.

The rejection under section 112 , first paragraph.

The Examiner has rejected Claims 1-20 on the grounds that the specification is not enabled for species of *Campylobacter* other than *C. jejuni* (see Page 3 in the Official Action), and that there was no experimental evidence presented (see Page 4 in the Official Action) for administration of more than one species of Campylobacter at one time, and rather (see Page 33 in the Official Action) that the invention is drawn to vaccination with *C. jejuni*.

Accordingly, and to facilitate prosecution herein, Applicant hereby amends to limit the claims to practice of the invention using C. jejuni only, which amendments are without prejudice to the representation of any cancelled subject matter by way of a continuation application. It is also noteworthty that the Examiner now agrees with the Applicant's characterization of Thoma et al (US6,440,408), i.e. that vaccination *in ovo* with live bacterial cells was expected to be unsafe, unless the bacterial cells where somehow attenuated, for example, by way of neutralizing antibodies (see the Official Action at Page 4). It is therefore respectfully believed that the section 112 rejection has been addressed.

The Section 103 rejections

As a preliminary matter, (see Pages 10-11 of the Official Action), the Examiner has apparently maintained the art rejections over Ziprin et al. and Noor et al. because the present Applicant's claims are deemed to only require production of "any type of immune response" (Page 11 top), and that a "vigorous immune response is not required by the instant claims", rather that "any type of immune response is encompassed regardless of its effectiveness" (page 11 middle) . Applicant respectfully traverses the rejection.

By its very language, Claim 1 requires an immune response which results from administration of an "immunizing effective amount". Those skilled in the art would recognize that" to immunize" does not mean to merely provide a dose of vaccine, it means to cause the subject to achieve some level of protection against a pathogen. Additionally, the Examiner is reading the term "immune response" too broadly, because "inducing an immune response" [Claim 1] is a specially defined term (see the Specification at Page 4, lines 33-38) wherein some **protective** result is required. To avoid any confusion, Applicant has herewith amended Claim 1 to make this point doubly clear. As a result, Applicant disagrees with the Examiner's contention (pages 10-11 in the Official Action) that Applicant's arguments are not commensurate in scope with the claimed invention. Therefore, Applicant reiterates its comments in the Reply of December 3, 2010, at Page 6 thereof:

"Second, Applicant has, in fact, correctly pointed out that Ziprin et al. is directed to colonization experiments, and persistent infection, which is not the same as whether or not any protective immune response has been achieved. "Inducing an immune response" as herein claimed is a specially defined term, provided at page 4, lines 33-37 of the present specification, and there is no demonstration or suggestion in Ziprin et al. that such a protective state has been achieved. Given that the persistently infected bird is harboring an organism that may in fact cause no harm whatsoever-- to the bird-- it is not clear that an immune response would *necessarily and reasonably* result, and Ziprin et al. does not so state."

Further, at Page 11 of the Official Action, the Examiner again correctly quotes from Applicant's prior response "No information can be found in this reference that teaches that in ovo delivery of a live strain of Campylobacter induces an immune response which provides some degree of protection against colonization". It is assumed that the Examiner now agrees with Applicant's comment, as the Examiner's response (page 11) is merely that [in Applicant's claims] there is no requirement for any special degree of immune response (page 11) although as we have now seen, Applicant's invention at all times requires a result of immuprotection.

In discussing the references that have been cited in support of rejections that have been made under 35 USC section 103, attention may first be directed to the previously cited article by G.C. Mead (World Poultry Science Journal, vol. 58, 2002, pp. 169-178), and which reflects the thinking of those skilled in the art as of June 2002. The *Mead* article points to additional factors recognized in the art, that additionally teach away from the present invention. Not only are live bacterial vaccines generally known to be unsafe for

administration to avian eggs (as the '408 patent clearly teaches), but *Campylobacter* species possess unusual growth and behavior characteristics.

Campylobacter are best characterized as microaerophiles that live in the mucosa of the intestine. As explained by Mead (see the Abstract, for example), *Campylobacter* rarely cause disease in poultry, and they are carried asymptomatically in the alimentary tract of affected birds. Successful colonization of the intestinal villi may also involve numerous other environmental factors, and host interactions, which are not well understood. There is, however, considerable evidence that *Campylobacter* infection in poultry can lead to human enteritis, and therefore preventing the spread of the bacterium in farm poultry is of great importance to human health. Although there are numerous approaches to providing bird flocks which are "Campylobacter-safe" (see Mead at 173) such as pre-colonizing the intestine with other competing bacterial species, there remains the clear problem that avian species are not to be *obviously* expected to mount vigorous immune responses against a microorganism that apparently causes them no harm., and even if an "immune response" is detected, is it of a kind that provides any practical effect and benefi?. Further, if such immunization is to be accomplished, the question is how. As a result, it will be seen that there is no combination of the references cited under 35 USC section 103 that credibly predicts that the present invention would be successful.

The Examiner has rejected all the claims under section 103 under a combination of *Noor et al.* and *Ziprin et al.* The rejection is respectfully traversed. Simply stated, there is nothing to combine, since, as the Examiner also notes, *Noor et al.* does not disclose live vaccines, and *Ziprin et al.* only discloses colonization experiments with live strains (including to elucidate the technical effects of mutations), with the intent of finding methods to prevent colonization, which is not obviously the same as causing and quantifying any effective immune state that may, or may not be detected.

More specifically, *Ziprin et al.* is directed to the role of some *Campylobacter jenuni* genes on cecal colonization , and liver invasion. *Ziprin et al.* also discloses the in ovo delivery of certain *C. jejuni* strains, and strains containing mutations, to chicken embryos. The subsequent effect on cecal colonization and liver invasion in 14-day old in ovo-challenged birds was also measured. No information can be found in this reference that teaches that in ovo delivery of a live strain of *Campylobacter* induces an immune response which provides some degree of protection against colonization. In fact, the reference teaches that the in ovo challenge route using live cells of *Campylobacter* can lead to persistently

infected birds.

Again referring to Mead (see at Page 171, first full paragraph, line 3), "although infection is associated with the production of specific immunoglobin (Cawthraw et al. 1994), these appear to have little or no effect on levels of intestinal carriage or the susceptibility to infection." Therefore, it is difficult to imagine that those skilled in the art would have concluded or even expected that the *in ovo* route would induce an immune response to infection, that is ultimately medically beneficial to human consumers, by actually protecting against intestinal colonization by *Campylobacter* in poultry. Indeed, Example 6 of the present specification is the first proof that reasonable success is possible, in regard of protecting against *Campylobacter* via live *in ovo* delivery to such immunologically immature animals, avian embryos.

At Page 6 of the Official Action, it is stated that "Noor et al. do not particularly exemplify the use of live Campylobacter strains in their methods". Applicant believes it would be more straightforward to say that Noor et al only disclose use of inactivated strains, thereby teaching away from the present invention. This teaching away is fully supported by Thoma et al. which specifically requires that any live bacterium should be coated with neutralizing antibodies prior to use in a vaccine. Ziprin et al., in fact makes no comment at all about whether any of its live *in ovo* experiments predicts an efficacious vaccine, Thus, the totality of the references does not therefore support a *prima facie* rejection, especially in regard of a large scale and dependable process which is safe for the immunized birds.

Applicant respectfully believes that it is not necessary to address the remaining rejections, which the Examiner will recognize are only directed to specific and straightforward features in certain dependent claims.

Conclusion

The present amendments are made for the purpose of advancing prosecution in conformity with Applicant's business plans. Applicant reserves the right to re-present claims directed to any cancelled subject matter by way of one or more continuation applications. The Patent Office is authorized to charge any needed fee, or fee deficiency, to Applicant's Deposit Account, No. 16-1445. An early and favorable action is respectfully requested.

Respectfully submitted,

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